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Case Report

Feasibility and Safety of Inducing Modest Hypothermia in Awake Patients With Acute Stroke Through Surface Cooling: A Case-Control Study

The Copenhagen Stroke Study

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Background and Purpose—Hypothermia reduces neuronal damage in animal stroke models. Whether hypothermia is neuroprotective in patients with acute stroke remains to be clarified. In this case-control study, we evaluated the feasibility and safety of inducing modest hypothermia by a surface cooling method in awake patients with acute stroke.

Methods—We prospectively included 17 patients (cases) with stroke admitted within 12 hours from stroke onset (mean 3.25 hours). They were given hypothermic treatment for 6 hours by the “forced air” method, a surface cooling method that uses a cooling blanket with a flow of cool air (10°C). Pethidine was given to treat compensatory shivering. Cases were compared with 56 patients (controls) from the Copenhagen Stroke Study matched for age, gender, initial stroke severity, body temperature on admission, and time from stroke onset to admission. Blood cytology, biochemistry, ECGs, and body temperature were monitored during hypothermic treatment. Multiple regression analyses on outcome were performed to examine the safety of hypothermic therapy.

Results—Body temperature decreased from $t_0=36.8^\circ\text{C}$ to $t_6=35.5^\circ\text{C}$ ($P<0.001$), and hypothermia was present until 4 hours after therapy ($t_0=36.8^\circ\text{C}$ versus $t_{10}=36.5^\circ\text{C}$; $P=0.01$). Mortality at 6 months after stroke was 12% in cases versus 23% in controls ($P=0.50$). Final neurological impairment (Scandinavian Stroke Scale score at 6 months) was mean 42.4 points in cases versus 47.9 in controls ($P=0.21$). Hypothermic therapy was not a predictor of poor outcome in the multivariate analyses.

Conclusions—Modest hypothermia can be achieved in awake patients with acute stroke by surface cooling with the “forced air” method, in combination with pethidine to treat shivering. It was not associated with a poor outcome. We suggest a large, randomized clinical trial to test the possible beneficial effect of induced modest hypothermia in unselected patients with stroke. (*Stroke*. 2000;31:2251-2256.)

Key Words: hypothermia ■ neuronal damage ■ neuroprotection ■ stroke

Neuronal damage is profoundly affected by alterations in body temperature in animal stroke models.¹⁻⁵ In humans, hypothermia serves as a neuroprotective procedure against cerebral hypoxia during neurosurgery and cardiovascular surgery.^{6,7} In traumatic brain injury, moderate hypothermia reportedly improves neurological outcome.⁸ In human stroke, low body temperature at admission is related to a lower mortality and better outcome in survivors.^{9,10} At present, we are aware of only 2 studies of intervention with mild hypothermia.^{11,12} Full anesthesia was part of the cooling procedure in these studies. This approach, however, limits active treatment with cooling to patients who are able to endure anesthesia. Furthermore, this procedure may put some patients at risk of arterial hypotension during anesthesia and will increase the need for intensive care resources extensively.

In the present study we investigated the possibility of achieving modest hypothermia, without the use of anesthesia, in awake patients with acute stroke. Even small differences in admission body temperature predict marked differences in outcome.^{9,10} We examined the feasibility and safety of reducing body temperature to approximately 35.5°C by the use of a surface cooling blanket in combination with pethidine to treat compensatory shivering. To test the safety of this method, outcome was compared with a group of matched control patients.

Subjects and Methods

We included 17 cases and 56 controls admitted within 12 hours from stroke onset to admission (mean 3.25 hours versus 4.5 hours). We have previously demonstrated body temperature on admission to be an independent predictor of stroke outcome up to 12 hours from

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onset, whereas body temperature beyond this time point had no prognostic significance.¹⁰ We excluded patients who used nitroglycerine at least once daily for cardiac angina; patients with signs of cardiac ischemia present, either on ECG obtained on admission or with precordial pain; patients with signs of cardiac incompensation; and patients with severe intermittent claudication, because severe atherosclerotic disease may contraindicate hypothermic therapy due to the increased cardiovascular demands from such treatment.¹³ Stroke was defined according to the World Health Organization criteria¹⁴: rapidly developed clinical signs of focal disturbance of cerebral function, lasting >24 hours or leading to death, with no apparent cause other than vascular origin. Subarachnoid hemorrhage was not included.

Directly upon admission the patients received hypothermic therapy for 6 hours by surface cooling by using the "forced air" method. We used the Bair Hugger Model 600 Polar Air, a unit that draws room air through a filter and cools the air to a specified temperature (in this study 10°C), and delivers the air via a hose to a blanket covering the patient. Hence, the surface of the body is cooled through the principle of convection. Body temperature was measured with 30-minute intervals together with blood pressure and pulse rate during hypothermic treatment. Body temperature was recorded on admission and during hypothermic therapy with a Diatek Model 9000 infrared aural thermometer. This device registers tympanic membrane temperature, which correlates well with body core temperature.¹⁵ We also recorded rectal temperature in the patients who underwent hypothermia and found full correlation between rectal and tympanic temperature readings. Compensatory shivering was treated with intravenous administration of pethidine in doses of 25 to 50 mg,¹⁶ given when the patient reported shivering or the investigator (L.P.K. or B.H.R.) observed shivering. All patients developed shivering at some point during cooling.

ECG recordings and blood tests were performed at the beginning of and at 3 and 6 hours during hypothermic therapy. One patient was withdrawn from hypothermic therapy after 5.5 hours because elevation of cardiospecific enzymes in blood tests (but not ECG recordings) indicated a possible acute myocardial infarction prior to treatment. Data from this patient are included in the analysis presented in this paper.

The following characteristics were preselected as possible outcome confounders: age, gender, body temperature on admission, initial stroke severity (Scandinavian Stroke Scale [SSS] score), time from stroke onset to admission, stroke subtype (hemorrhagic versus infarction), diabetes, previous myocardial infarction, hypertension, intermittent claudication, atrial fibrillation, daily alcohol consumption, and daily smoking. The classification of the specific factors was as follows. *Stroke severity*: the SSS was used to assess initial stroke severity (measured at the time of acute admission) and final neurological impairment (6 months after).^{17,18} The SSS evaluates, on a total score from 0 to 58 points, level of consciousness; eye movement; power in the arm, hand, and leg; orientation; aphasia; facial paresis; and gait. *Diabetes*: if present before admission, or diagnosed during hospital stay, or plasma glucose level of >11 mmol/L on admission, according to the WHO diagnostic criteria for diabetes.¹⁹ *Atrial fibrillation*: if present on admission ECG. *Hypertension*: ongoing antihypertensive treatment at the time of admission. *Stroke subtype* (infarct versus hemorrhage): verified by cerebral CT in all patients. *Infection*: diagnosed within 3 days of admission if clinically present or if discovered by radiological examination of the chest or analysis of urine (routinely performed for all patients on the day of admission). *Mortality*: measured at 28 days after stroke and at 6-month follow-up.

The control patients were selected from our stroke database, the Copenhagen Stroke Study, which comprises detailed data on 1197 stroke patients. The design of the study has been described in detail elsewhere.^{20,21} Each case was individually matched by the following principles to the patients in the control group: initial stroke severity ± 4 points on the SSS scale, body temperature on admission $\pm 0.5^\circ\text{C}$, age of the patient ± 5 years, and gender. All controls matching each case were selected in an effort to avoid selection bias.

Statistical analyses were performed with the SPSS statistical package for Windows.²² Univariate statistics were performed by nonparametric tests: the Wilcoxon signed rank test for comparison of continuous data and Fisher exact test for crosstab statistics between 2 groups of cases. The effect of hypothermic treatment on mortality, independent of possible outcome confounders (ie, age, gender, body temperature on admission, initial stroke severity, stroke subtype, diabetes, previous myocardial infarction, hypertension, intermittent claudication, atrial fibrillation, daily alcohol consumption, and smoking), was tested in a multiple logistic regression model. All variables were included in the model by using the backward procedure. Unimportant variables were removed one by one until only variables with a value of $P < 0.2$ remained. The analysis was then performed with the forward procedure. The 2 methods of multiple regression analysis, backward and forward, often yield the same model, but differences are not uncommon. Neither approach is more correct than the other. The 2 methods yielded similar models. The effect of hypothermic treatment on final neurological impairment, independent of the above-mentioned possible outcome confounders, was tested in a multiple linear regression model. All variables were included in the model using the backward procedure. Unimportant variables were removed one by one until only variables with a value of $P < 0.2$ remained. The analysis was then performed with the forward procedure. The 2 methods yielded similar models. Assumption of linearity was checked by plotting standardized residuals against standardized predicted values as well as against independent variables and by regression plots. The distribution of residuals was examined by histograms for standardized residuals and by normal probability plots. The required 2-tailed level of significance for all tests was set at 0.05. The study was approved by the Ethics Committee of Copenhagen, approval No. KF 01-117/97. Written informed consent was obtained from either the patients or their relatives, the latter only in patients who were not fully conscious.

Results

Basic characteristics are given in Table 1. None of the basic variables differed significantly between cases and controls. The Figure shows body temperature as a function of time during and after hypothermic therapy. A significantly lower mean body temperature was achieved after 1 hour of hypothermic therapy ($t_0 = 36.8^\circ\text{C}$ versus $t_1 = 36.4^\circ\text{C}$, $P = 0.002$). Lowest mean body temperature was achieved after 6 hours ($t_0 = 36.8^\circ\text{C}$ versus $t_6 = 35.5^\circ\text{C}$, $P < 0.001$). Significant hypothermia was present until 4 hours after cessation of hypothermic therapy (mean $t_0 = 36.8^\circ\text{C}$ versus $t_{10} = 36.5^\circ\text{C}$, $P = 0.01$).

Administration of pethidine to eliminate shivering was largely dependent on the demands of the patients. The total mean dose of pethidine given per patient throughout the 6 hours of hypothermic therapy was 241 mg.

Data of vital signs, blood cytology, and blood biochemistry are given in Table 2. Hematocrit increased significantly during hypothermia from a mean of 0.43 to 0.46 ($P < 0.01$). Accordingly, mean hemoglobin concentration increased as well, from 9.0 mmol/L to 9.6 mmol/L during hypothermic therapy ($P < 0.01$). Potassium concentration increased from mean 3.6 mmol/L to 4.1 mmol/L of plasma ($P < 0.01$). The mean plasma concentration of albumin increased from 41.0 mmol/L to 43.7 mmol/L ($P < 0.01$). The mean concentration of creatine kinase increased from 124 to 164 ($P = 0.01$). Activated fibrinogen in plasma showed a rise from mean 12.2 to 13.2 ($P = 0.02$). Mean level of C-reactive protein increased from 12.7 to 18.7 during hypothermic therapy ($P = 0.03$). Data of vital signs during hypothermic therapy

TABLE 1. Basic Characteristics of Cases Versus Controls

	+Hypothermia	-Hypothermia	P
Patients, n	17	56	
Sex, male/female	12/5 (70.6%)	43/13 (76.8%)	0.60
Age, y (SD)	68.6 (16.0)	70.1 (10.1)	0.72
Body temperature on admission, °C (SD)	36.8 (0.6)	36.9 (0.4)	0.76
Initial stroke severity* (SD)	25.8 (11.5)	28.0 (11.5)	0.50
Time from stroke onset to admission, h (SD)	3.25 (4.24)	4.50 (3.50)	0.35
Stroke subtype, infarction	11/6 (64.7%)	33/15 (68.8%)	0.76
Diabetes	3/14 (17.6%)	12/44 (21.4%)	0.74
Previous acute myocardial infarction	2/14 (11.8%)	6/48 (11.1%)	0.89
Ischemic heart disease	2/15 (11.8%)	17/38 (30.9%)	0.12
Hypertension	7/10 (41.2%)	17/35 (32.7%)	0.52
Intermittent claudication	3/14 (17.6%)	7/45 (13.5%)	0.67
Atrial fibrillation	2/15 (11.8%)	11/45 (19.6%)	0.46
Daily alcohol consumption	6/11 (35.6%)	24/28 (46.2%)	0.43
Smoking	9/8 (52.9%)	28/22 (56.0%)	0.83

+Hypothermia indicates cases; -Hypothermia, controls.

*SSS score.

showed no significant changes in mean diastolic blood pressure; however, mean systolic blood pressure decreased from 178 mm Hg to 169 mm Hg ($P=0.02$). The mean pulse rate decreased from 72 to 68 beats/min ($P=0.02$).

None of the patients showed signs of significant cardiac arrhythmias or cardiac ischemia on consecutive ECG recordings performed during hypothermic therapy.

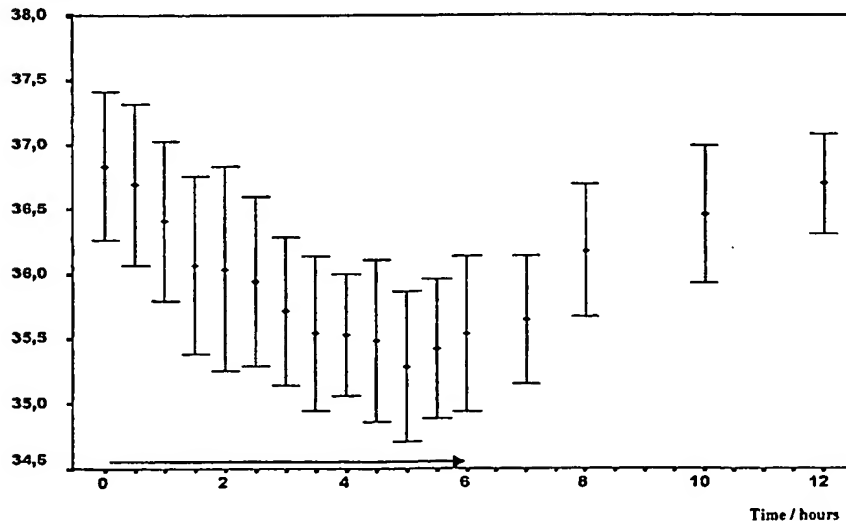
End point characteristics are stated in Table 3. The frequency of infectious complications was 18% in the patients who underwent hypothermic therapy compared with 13% in the control group ($P=0.7$). In a multiple logistic regression analysis adjusted for age, time from stroke onset to admission, stroke severity on admission, body temperature on admission, gender, and hypothermic therapy, only female gender ($P=0.04$) and increasing time from stroke onset to

admission ($P<0.01$), but not hypothermic therapy ($P=0.3$), were significant for the presence of infectious complications within the first 3 days of admission.

Final neurological impairment was 42.4 points in SSS score in patients undergoing active hypothermia versus 47.9 points in the control group ($P=0.2$). When adjusted for factors such as age, time from stroke onset to admission, stroke severity on admission, body temperature on admission, and gender in a multivariate linear regression model, hypothermic therapy was not an independent predictor of neurological outcome ($P=0.2$).

Mortality at 28 days was 6% in the patients who underwent hypothermic therapy versus 11% in the control group (univariate $P=0.5$). Six-month mortality was 12% in patients undergoing hypothermic therapy versus 23% in controls

Body temperature / °C



Consecutive measurements of body temperature (tympanic) during and after hypothermic therapy (n=17). Vertical bars indicate standard deviations and arrow indicates duration of hypothermic therapy.

TABLE 2. Vital Signs, Blood Cytology, and Biochemistry During Hypothermia

	t=0 h	t=3 h	t=6 h	P
Hemoglobin concentration, mmol/L	9.0 (1.4)	9.4 (1.3)	9.6 (1.2)	0.005
F _{hbc}	0.43 (0.07)	0.45 (0.06)	0.46 (0.02)	0.007
Leukocyte count, 10 ⁹ /L	10.6 (4.3)	10.3 (3.7)	10.4 (3.7)	0.92
Lymphocyte count, 10 ⁹ /L	1.7 (0.9)	1.7 (0.9)	1.8 (0.8)	0.41
Platelet count, 10 ⁹ /L	216 (99)	216 (100)	221 (97)	0.62
Potassium concentration, mmol/L	3.6 (0.4)	3.9 (0.6)	4.1 (0.7)	0.009
Sodium concentration, mmol/L	140 (4.2)	141 (3.9)	141 (4.5)	0.06
Albumin concentration, g/L	41.0 (4.1)	42.8 (4.1)	43.7 (4.3)	0.001
Glucose concentration, mmol/L	9.2 (4.0)	8.9 (3.8)	8.9 (3.8)	0.44
Creatine kinase, U/L	124 (130)	144 (152)	164 (194)	0.01
ASAT, U/L	101 (297)	92 (253)	88 (234)	0.08
LDH, U/L	448 (317)	446 (152)	443 (222)	0.10
Clotting factors 2, 7, and 10	0.87 (0.22)	0.88 (0.21)	0.86 (0.19)	0.28
aPTT, s	28.1 (5.0)	28.1 (5.0)	28.6 (6.1)	0.20
Activated fibrinogen, μ mol/L	12.2 (3.7)	12.9 (3.6)	13.2 (3.7)	0.02
Antithrombin III	0.96 (0.20)	0.98 (0.20)	0.98 (0.20)	0.33
C-reactive protein, mg/L	12.7 (18.1)	16.3 (24.6)	18.7 (28.8)	0.03
Blood pressure, mm Hg				
Diastolic	100 (23)	102 (19)	97 (21)	0.22
Systolic	178 (31)	175 (27)	169 (29)	0.02
Pulse rate, beats/min	72 (11)	70 (11)	68 (11)	0.02

Values in paranthesis are SD. F_{hbc} indicates hematocrit; ASAT, aspartate aminotransferase; LDH, lactate dehydrogenase; and aPTT, activated partial thromboplastin time.

($P=0.3$). In a multiple logistic regression model of mortality at 28 days and 6 months after stroke, adjusted for age, time from stroke onset to admission, stroke severity on admission, body temperature on admission, gender, and hypothermic therapy, hypothermia was not an independent predictor of mortality at 28 days ($P=0.4$) or at 6 months ($P=0.2$).

Discussion

In the present study, we were able to decrease body temperature in awake stroke patients by a mean of 1.3°C through whole body surface cooling and without the use of anesthesia. Significant hypothermia was achieved rapidly and maintained for several hours after cessation of hypothermic therapy. Previous studies on hypothermia in humans have reported an increase in body temperature after hypothermia. However, no such increase was observed in the present study. A possible explanation could be the relatively smaller decrease in body

temperature in this study compared with those in previous reports.²³

Hemoconcentration occurred during hypothermia. The mechanism for this is not known, although it may result from vasoconstriction of peripheral blood vessels in response to surface cooling. This may also explain the increase found in albumin concentration. Potassium ion concentration and the concentration of creatine kinase also increased. These changes may be explained by the shivering that was seen in response to cooling, because muscle fiber activation causes these substances to increase in peripheral blood. We observed an increase of C-reactive protein and activated fibrinogen. Whether this is a response to stroke or to hypothermic therapy is not known.

Most of the patients included in this study were fully conscious during hypothermia. However, none experienced side effects to such a degree that they wanted to withdraw from further participation in the study. The most uncomfortable events during hypothermia, as reported by the patients, appeared to be the shivering episodes, and pethidine was mandatory to treat shivering and achieve hypothermia. In general, the method appeared to be well tolerated by the patients. Furthermore, we had no incidents of cardiac ischemic events as monitored by ECG recordings and no increase in the frequency of infections in the hypothermia group. Even though we found a slight decrease in pulse rate and systolic (but not diastolic) blood pressure, this did not seem to affect the outcome in the hypothermia patients in either the short- or

TABLE 3. Infection, Mortality, and Outcome in Cases/Controls

	+Hypothermia	-Hypothermia	P
Infections	3/14 (18%)	7/49 (13%)	0.70
Stroke severity, 6 months* (SD)	42.4 (13.7)	47.9 (11.4)	0.21
Mortality, 28 d	1/16 (6%)	6/50 (11%)	0.50
Mortality, 6 mo	2/15 (12%)	13/43 (23%)	0.31

+Hypothermia indicates cases; -Hypothermia, controls.

*SSS score.

the long-term perspective. No systematic recording of breath rate was performed.

We know of only 2 previous reports^{11,12} that have investigated active hypothermia in acute stroke patients. In both studies, moderate hypothermia (33°C) was induced in patients with severe stroke caused by middle cerebral artery occlusion. The patients were admitted to an intensive care unit for surgical treatment of increased intracranial pressure, and anesthesia was used. The method used to achieve hypothermia was whole body surface cooling in combination with cold infusions. In one of the studies,¹² information on complication frequency and outcome was given. The predominant complication to hypothermia was pneumonia in 40%, and the overall survival rate in the 25 patients was 56%. Outcome at 3 months appeared favorable and was mean 38 points on the SSS. However, no control group was included in these studies. In the present study, we focused on the possibility of inducing hypothermia in awake patients without the use of anesthesia. If anesthesia were necessary to achieve hypothermia, hypothermic treatment would most likely be restricted to a small number of patients. Furthermore, if anesthesia were required, large investments would be necessary to reorganize stroke treatment, and hypothermia would be offered only in highly specialized units. We therefore created a model for inducing modest hypothermia that will be easily applicable in most hospital wards which treat patients with acute stroke. If proved efficient, this will enable such treatment to perhaps benefit the stroke population in general.

The mechanisms for a possible neuroprotective effect of hypothermia are largely unknown. In human ischemic stroke, a central core of irreversibly damaged brain tissue is surrounded by an area of tissue with hypoperfusion—the “ischemic penumbra.”²⁴ In this zone of hypoperfused brain tissue, neurons are potentially salvageable if reperfusion is established in time. Hence, a time window exists for saving neuronal tissue. We have previously reported (in the Copenhagen Stroke Study^{9,10}) that body temperature independently predicts recovery, lesion size on CT scans, and mortality up to 12 hours after stroke onset (but not after this time point). Others,²⁵ confirming our findings, have suggested that the time window for temperature modulation may be even wider. Hypothermia decreases metabolic rate and may thereby decrease lactacidosis in the penumbra, whereas hyperthermia increases lactacidosis with accelerating neuronal death.²⁶ In animal models of ischemic stroke, hypothermia attenuates postischemic release of the excitotoxic neurotransmitters glutamic acid and aspartic acid, which are thought to cause exhaustion of surrounding postsynaptic neurons and delayed neuronal death.^{27,28} This release of amino acids has recently been confirmed in a study of human stroke by Castillo et al.²⁹ Among the mechanisms suggested to be influenced by hypothermia are free radical production and damage to the blood-brain barrier.²⁶

In conclusion, modest hypothermia can be achieved without anesthesia in awake patients with acute stroke by use of the “forced air” method, and it is not associated with a poorer outcome in patients who receive hypothermic therapy than in matched controls. A randomized clinical trial on modest hypothermia in acute stroke is needed to further investigate

this method that seems low in cost and easily applicable in most stroke units.

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